Welcome to STN International! Enter x:x

LOGINID:sssptaul25txc

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),

```
                AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
 NEWS HOURS     STN Operating Hours Plus Help Desk Availability
 NEWS INTER     General Internet Information
 NEWS LOGIN     Welcome Banner and News Items
 NEWS PHONE     Direct Dial and Telecommunication Network Access to STN
 NEWS WWW       CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:23:08 ON 20 MAY 2003

=> s vanadium and sulfonylurea?
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> file uspatfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'USPATFULL' ENTERED AT 14:23:41 ON 20 MAY 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 15 May 2003 (20030515/PD)
FILE LAST UPDATED: 15 May 2003 (20030515/ED)
HIGHEST GRANTED PATENT NUMBER: US6564383
HIGHEST APPLICATION PUBLICATION NUMBER: US2003093849
CA INDEXING IS CURRENT THROUGH 15 May 2003 (20030515/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 15 May 2003 (20030515/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together         <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to           <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
```

```
>>>  the earliest to the latest publication.                              <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s canadium and sulfonylurea
           21 CANADIUM
         2209 SULFONYLUREA
L1          0 CANADIUM AND SULFONYLUREA

=> s vanadium and sulfonylurea
        40027 VANADIUM
         2209 SULFONYLUREA
L2         61 VANADIUM AND SULFONYLUREA

=> s vanadium and sulfonylurea?
        40027 VANADIUM
         3488 SULFONYLUREA?
L3        104 VANADIUM AND SULFONYLUREA?

=> s l3 and 10mg
          609 10MG
L4          0 L3 AND 10MG

=> s l3 and 15mg
          163 15MG
L5          0 L3 AND 15MG

=> s l3 and diabetes
        24701 DIABETES
L6        100 L3 AND DIABETES

=> s l6 and mg
       305571 MG
L7         95 L6 AND MG

=> s l7 and pd <1998
      2268293 PD <1998
                (PD<19980000)
L8          3 L7 AND PD <1998

=> d l8 1-3

L8   ANSWER 1 OF 3  USPATFULL
AN     2001:168152  USPATFULL
TI     Substituted n-(indole-2-carbonyl-) amides and derivatives as glycogen
       phosphorylase inhibitors
IN     Hulin, Bernard, Essex, CT, United States
       Hoover, Dennis J., Stonington, CT, United States
       Treadway, Judith L., Gales Ferry, CT, United States
       Martin, William H., Essex, CT, United States
PA     Pfizer Inc., New York, NY, United States (U.S. corporation)
PI     US 6297269         B1   20011002
       WO 9639385  19961212                                              <--
AI     US 1997-952668          19971202 (8)
       WO 1995-IB443           19950606
                               19971202  PCT 371 date
                               19971202  PCT 102(e) date
DT     Utility
FS     GRANTED
LN.CNT 4318
INCL   INCLM: 514/414.000
```

INCLS: 548/491.000; 548/492.000
NCL NCLM: 514/414.000
NCLS: 548/491.000; 548/492.000
IC [7]
ICM: A01N043-38
ICS: C07D209-10; C07D209-42
EXF 548/492; 548/491; 548/414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 3 USPATFULL
AN 2000:109834 USPATFULL
TI Substituted n-(indole-2-carbonyl)-glycinamides and derivatives as glycogen phosphorylase inhibitors
IN Hoover, Dennis J., Stonington, CT, United States
Hulin, Bernard, Essex, CT, United States
Martin, William H., Essex, CT, United States
Phillips, Douglas, Gales Ferry, CT, United States
Treadway, Judith L., Gales Ferry, CT, United States
PA Pfizer, Inc., New York, NY, United States (U.S. corporation)
PI US 6107329 20000822
WO 9639384 19961212 <--
AI US 1997-952669 19971202 (8)
WO 1995-IB442 19950606
19971202 PCT 371 date
19971202 PCT 102(e) date
DT Utility
FS Granted
LN.CNT 5662
INCL INCLM: 514/415.000
INCLS: 514/018.000; 514/419.000; 514/235.200; 514/323.000; 514/330.000; 514/385.000; 548/100.000
NCL NCLM: 514/415.000
NCLS: 514/018.000; 514/235.200; 514/323.000; 514/330.000; 514/385.000; 514/419.000; 548/100.000
IC [7]
ICM: A01N043-38
ICS: A01N043-40; A01N043-52; A61K031-405
EXF 514/18; 514/415; 514/419; 514/235.2; 514/323; 514/330; 514/385; 548/100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 3 OF 3 USPATFULL
AN 94:28742 USPATFULL
TI Complexed **vanadium** for the treatment of **diabetes** mellitus
IN McNeill, John H., Delta, Canada
Hoveyda, Hamid R., Vancouver, Canada
Orvig, Chris, Vancouver, Canada
PA The University of British Columbia, Vancouver, Canada (non-U.S. corporation)
PI US 5300496 19940405 <--
AI US 1991-767510 19910930 (7)
DT Utility
FS Granted
LN.CNT 459
INCL INCLM: 514/186.000
INCLS: 514/492.000; 514/884.000
NCL NCLM: 514/186.000
NCLS: 514/492.000; 514/884.000
IC [5]
ICM: A61K031-555
ICS: A61K031-28
EXF 514/184; 514/186; 514/492; 514/884

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l81-3 kwic
'L999-3' IS NOT A VALID FORMAT FOR FILE 'USPATFULL'

The following are valid formats:

The default display format is STD.

ABS -------- AB
ALL -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
EXF, ARTU
ALLG ------- ALL plus PAGE.DRAW
BIB -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD, RLI,
PRAI, DT, FS, EXNAM, LREP, CLMN, ECL, DRWN, LN.CNT
BIB.EX ----- BIB for original and latest publication
BIBG ------- BIB plus PAGE.DRAW
BROWSE ----- See "HELP BROWSE" or "HELP DISPLAY BROWSE". BROWSE must
entered on the same line as DISPLAY, e.g., D BROWSE.
CAS -------- OS, CC, SX, ST, IT
CBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PRAI, DT, FS
DALL ------- ALL, delimited for post-processing
FP --------- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI, RLI,
PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL,
NCLM, NCLS, EXF, REP, REN, ARTU, EXNAM, LREP,
CLMN, DRWN, AB
FP.EX ------ FP for original and latest publication
FPALL ------ PI, TI, IN, INA, PA, PAA, PAT, PETRM, DCD, AI,
RLI, PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL, NCLM,
NCLS, EXF, REP, REN,ARTU, EXNAM, LREP, CLMN, DRWN, AB,
PARN, SUMM, DRWD, DETD, CLM
FPBIB ------ PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI,
RLI, PRAI, REP, REN, EXNAM, LREP, CLM, CLMN, DRWN
FHITSTR ---- HIT RN, its text modification, its CA index name, and
its structure diagram
FPG -------- FP plus PAGE.DRAW
GI --------- PN and page image numbers
HIT -------- All fields containing hit terms
HITRN ------ HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
its structure diagram
IABS ------- ABS, indented with text labels
IALL ------- ALL, indented with text labels
IALLG ------ IALL plus PAGE.DRAW
IBIB ------- BIB, indented with text labels
IBIB.EX ---- IBIB for original and latest publication
IBIBG ------ IBIB plus PAGE.DRAW
IMAX ------- MAX, indented with text labels
IMAX.EX ---- IMAX for original and latest publication
IND -------- INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
EXF, ARTU, OS, CC, SX, ST, IT
ISTD ------- STD, indented with text labels
KWIC ------- All hit terms plus 20 words on either side
MAX -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
EXF, ARTU OS, CC, SX, ST, IT

```
MAX.EX ----- MAX for original and latest publication
OCC -------- List of display fields containing hit terms
SBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
             DT, FS, LN.CNT
SCAN ------- AN, TI, NCL, NCLM, NCLS, IC, ICM, ICS (random display
             without answer number.  SCAN must be entered on the
             same line as DISPLAY, e.g., D SCAN)
STD -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
             DT, FS, LN.CNT, INCL, INCLM, INCLS, NCL, NCLM, NCLS,
             IC, ICM, ICS, EXF (STD is the default)
STD.EX ----- STD for original and latest publication
TRIAL ------ AN, TI, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC,
             ICM, ICS

ENTER DISPLAY FORMAT (STD):std

L8   ANSWER 1 OF 3  USPATFULL
AN     2001:168152  USPATFULL
TI     Substituted n-(indole-2-carbonyl-) amides and derivatives as glycogen
       phosphorylase inhibitors
IN     Hulin, Bernard, Essex, CT, United States
       Hoover, Dennis J., Stonington, CT, United States
       Treadway, Judith L., Gales Ferry, CT, United States
       Martin, William H., Essex, CT, United States
PA     Pfizer Inc., New York, NY, United States (U.S. corporation)
PI     US 6297269         B1   20011002
       WO 9639385  19961212                                          <--
AI     US 1997-952668          19971202 (8)
       WO 1995-IB443           19950606
                               19971202  PCT 371 date
                               19971202  PCT 102(e) date
DT     Utility
FS     GRANTED
LN.CNT 4318
INCL   INCLM: 514/414.000
       INCLS: 548/491.000; 548/492.000
NCL    NCLM:  514/414.000
       NCLS:  548/491.000; 548/492.000
IC     [7]
       ICM: A01N043-38
       ICS: C07D209-10; C07D209-42
EXF    548/492; 548/491; 548/414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d l8 1-3 kwic

L8   ANSWER 1 OF 3  USPATFULL
PI     US 6297269         B1   20011002
       WO 9639385  19961212                                          <--
SUMM   This invention relates to glycogen phosphorylase inhibitors,
       pharmaceutical compositions containing such inhibitors and the use of
       such inhibitors to treat diabetes, hyperglycemia,
       hypercholesterolemia, hypertension, hyperinsulinemias, hyperlipidemia,
       atherosclerosis and myocardial ischemia in mammals.
SUMM   In spite of the early discovery of insulin and its subsequent widespread
       use in the treatment of diabetes, and the later discovery of
       and use of sulfonylureas (e.g. Chlorpropamide.TM. (Pfizer),
       Tolbutamide.TM. (Upjohn), Acetohexamide.TM. (E. I. Lilly),
       Tolazamide.TM. (Upjohn)) and biguanides (e.g. Phenformin.TM. (Ciba
       Geigy), Metformin.TM. (G. D. Searle)) as oral hypoglycemic agents, the
       treatment of diabetes remains less than satisfactory. The use
```

of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type I **diabetes**, insulin dependent **diabetes** mellitus), requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of. . . causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death. Treatment of non-insulin dependent **diabetes** mellitus (Type II **diabetes**, NIDDM) usually consists of a combination of diet, exercise, oral agents, e.g. **sulfonylureas**, and in more severe cases, insulin. However, the clinically available hypoglycemics can have other side effects which limit their use.. . .

SUMM . . . whom the causative agent or disorder is unknown. While such "essential" hypertension is often associated with disorders such as obesity, **diabetes** and hypertriglyceridemia, the relationship between these disorders has not been elucidated. Additionally, many patients display the symptoms of high blood. . .

SUMM This invention is directed to glycogen phosphorylase inhibitor compounds of Formula I useful for the treatment of **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM Yet another aspect of this invention is directed to a method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a Formula I compound.

SUMM . . . to a mammal suffering from hypercholesterolemia a hypercholesterolemia treating amount of a Formula I compound. Included in the treatment of **diabetes** is the prevention or attenuation of long term complications such as neuropathy, nephropathy, retinopathy or cataracts.

SUMM Another aspect of this invention is directed to pharmaceutical compositions for the treatment of **diabetes** which comprise a therapeutically effective amount of a glycogen phosphorylase inhibitor;

SUMM . . . or more antidiabetic agents such as insulin and insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2 ; **Sulfonylureas** and Analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide.RTM., glimepiride, repaglinide, meglitinide; Biguanides: metformin, phenformin, buformin; .alpha.2-Antagonists and Imidazolines: midaglizole, isaglidole,. . . 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243; Phosphodiesterase Inhibitors: L-386,398; Lipid-lowering Agents: benfluorex; Antiobesity Agents: fenfluramine; Vanadate and **vanadium** complexes (e.g. naglivan.RTM.) and peroxovanadium complexes; Amylin Antagonists; Glucagon Antagonists; Gluconeogenesis Inhibitors; Somatostatin Analogs; Antilipolytic Agents: nicotinic acid, acipimox, WAG. . .

SUMM Another aspect of this invention is a method of treating **diabetes** in a mammal with the above described combination compositions.

SUMM . . . glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity. Examples include **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM . . . of 10 g tryptone, 5 g yeast extract, 5 g NaCl, and 1 ml 1N NaOH per liter) plus 100 **mg**/L ampicillin, 100 **mg**/L pyridoxine and 600 **mg**/L MnCl.sub.2 and grown at 37.degree. C. to a cell density of OD.sub.550 =1.0. At this point, the cells are induced. . .

SUMM . . . immobilized on Affi-Gel 10 (BioRad Corp., Melvile, N.Y.) as per the manufacturer's instructions. In brief, the phosphorylase kinase enzyme (10 **mg**) is incubated with washed Affi-Gel beads (1 mL)

in 2.5 mL of 100 mM HEPES and 80 mM CaCl.sub.2 at. . .

SUMM . . . PO.sub.4 and 0.5 mM dithiothreitol. 20 .mu.l of this stock is added to 80 .mu.l of Buffer A containing 0.47 **mg**/mL glycogen, 9.4 mM glucose, 0.63 mM of the oxidized form of nicotinamide adenine dinucleotide phosphate (NADP.sup.+). The compounds to be. . .

SUMM . . . MgCl.sub.2 and 0.5 mM dithiothreitol. 20 .mu.L of this stock is added to 80 .mu.L of Buffer B with 1.25 **mg**/mL glycogen, 9.4 mM glucose, and 0.63 mM glucose-1-phosphate. The compounds to be tested are added as 5 .mu.L of solution. . . J., Reinach, P. S. and Candia, O. A. (1979) Anal. Biochem. 100, 95-97] modified as follows: 150 .mu.L of 10 **mg**/mL ammonium molybdate, 0.38 **mg**/mL malachite green in 1 N HCl is added to 100 .mu.L of the enzyme mix. After a 20 minute incubation. . .

SUMM . . . (a modification of the method of Richterich and Dauwalder, Schweizerische Medizinische Wochenschrift, 101, 860 (1971)) (hexokinase method) using a 100 **mg**/dL standard. Plasma glucose is then calculated by the equation:

SUMM Plasma glucose (**mg**/dL)=Sample value.times.5.times.1.784=8.92.t imes.Sample value

SUMM The animals dosed with vehicle maintain substantially unchanged hyperglycemic glucose levels (e.g., greater than or equal to 250 **mg**/dL), animals treated with test compounds at suitable doses have significantly depressed glucose levels. Hypoglycemic activity of the test compounds is. . .

SUMM . . . administered, the animals are sacrificed by decapitation and trunk blood is collected into 0.5 mL serum separator tubes containing 3.6 **mg** of a 1:1 weight/weight sodium fluoride: potassium oxalate mixture. The freshly collected samples are centrifuged for two minutes at 10,000.times.g. . .

SUMM . . . method; a modification of the method of Allain, et al. Clinical Chemistry 20, 470 (1974)) using a 100 and 300 **mg**/dL standards. Serum insulin, triglycerides, and total cholesterol levels are then calculated by the equations,

SUMM Serum triglycerides (**mg**/dL)=Sample value.times.2

SUMM Serum total cholesterol (**mg**/dL)=Sample value.times.2

SUMM The animals dosed with vehicle maintain substantially unchanged, elevated serum insulin (e.g. 225 .mu.U/mL), serum triglycerides (e.g. 225 **mg**/dl), and serum total cholesterol (e.g. 160 **mg** /dL) levels, while animals treated with test compounds of this invention generally display reduced serum insulin, triglycerides, and total cholesterol levels.. . .

SUMM . . . BB/W rats, or non-diabetic BB/W age matched control rats are pretreated with heparin (1000 u, i.p.), followed by pentobarbital (65 **mg**/kg, i.p.). After deep anesthesia is achieved as determined by the absence of a foot reflex, the heart is rapidly excised. . .

SUMM Surgery: New Zealand White male rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 **mg**/kg, i.v.). A tracheotomy is performed via a ventral midline cervical incision and the rabbits are ventilated with 100% oxygen using. . .

SUMM . . . over, for example 5 minutes and allowing 10 minutes before further intervention or by infusing the adenosine agonist, PIA (0.25 **mg**/kg). Following ischemic preconditioning, pharmacological preconditioning or no conditioning (unconditioned, vehicle control) the artery is occluded for 30 minutes and then. . .

SUMM . . . lowering activities and hyperinsulinemia reversing activities of the compounds of this invention is in the range of 0.005 to 50 **mg**/kg/day, preferably 0.01 to 25 **mg**/kg/day and most preferably 0.1 to 15 **mg**/kg/day.

DETD . . . polar material characterized by .sup.1 H NMR as the corresponding N, O-bis (5-chloro-1H-indole-2-carbonyl derivative. The more polar desired substance (48 **mg**) was dissolved in a mixture of methanol and 0.25 mL 1N HCl, the resulting solution

concentrated, and the resulting solid triturated with ether giving the title substance (42 **mg**): HPLC (70/30) 80%, 2.53 minutes and 13%, 4.04 min, the latter corresponding in retention time to the N,O-bis O-acylated derivative. . .

DETD . . . at 25.degree. C. for 0.5 hours. The mixture was concentrated and the residue triturated with ether and dried: Yield 212 **mg**; HPLC (15/85) 2.85 min; PBMS 278 (MH+, 100%).

DETD N-Methylpiperazine (75 **mg**, 0.75 mmol) and (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-4-phenyl-butyric acid (0.200 g, 0.68 mmol) were coupled according to Procedure A giving a colorless foam which was used without purification: Yield 225 **mg**, 88%; PBMS 378 (MH+, 100%);

DETD . . . A (except at 0-25.degree. C.). The crude product was dissolved in dichloromethane and the resulting solution stirred with approx 200 **mg** dimethylaminopyridine-polystyrene resin (Aldrich Chemical Co., Milwaukee, Wis.) for 1 hour, filtered, and concentrated giving the product as a colorless solid:. . .

DETD {(1S)-[(R)-Hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-carbamic acid tert-butyl ester (791 **mg**, 2.3 mmol) was dissolved in 4M HCl-dioxanes for 45 minutes at 25.degree. C. for 45 min, the mixture concentrated, the residue coevaporated with ether, suspended in ether and filtered giving 583 **mg** (91%) of the title substance.

DETD . . . with 6N HCl and extracted with ethyl acetate. The extracts were dried and concentrated giving a light brown solid (458 **mg**, 34%): HPLC (60/40) 5.31 (93%).

DETD . . . acid (40 mL) and cooled giving a solid which was filtered, washed with cold ethyl acetate and dried: Yield 980 **mg** 70%; HPLC (60/40) 3.09 minutes (97%).

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-4-phenyl-butyric acid (357 **mg**, 1.0 mmol) and N,O-dimethylhydroxylamine hydrochloride, 98% (98 **mg**, 1.0 mmol) were coupled according to procedure A (dimethylformamide solvent). The foam obtained was triturated with ether, the sticky solid dissolved in dichloromethane, concentrated and triturated with hexanes: yield 215 **mg**, 54%; HPLC (60/40) 6.38 minutes (98%);PBMS 400/402 (MH+, 100%);

DETD . . . the mixture was filtered and the filtrate carried on in the usual manner of Procedure A). The crude product (920 **mg**) was dissolved in methanol and treated with 1N NaOH (6.6 mL) for 2 hours at 25.degree. C. 1N NaOH was. . . brine, dried, and concentrated. The resulting colorless solid was stirred in chloroform and filtered giving the title substance: Yield 763 **mg**, 40%; HPLC (60/40) 2.86 minutes (89%); mp 214-215.degree. C.; PBMS 283/285 (MH+, 100%); .sup.1 H NMR (DMSO-d.sub.6) .delta.11.78 (s, 1H),. . .

DETD (1S,2R)-(1-Benzyl-2-dimethylcarbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (283 **mg**, 0.84 mmol) was dissolved in 4N HCl-dioxane (1 mL) for 1.5 hours at 25.degree. C., concentrated and the residue coevaporated. . .

DETD Sodium hydride-oil dispersion (53 **mg** of 50%) was added to a solution of (1S,2R)-(1-benzyl-2-dimethylcarbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (322 **mg**, 1.0 mmol) in tetrahydrofuran (4 mL) at 0.degree. C. After effervescence ceased (several minutes), methyl iodide (155 **mg**) was added, and after 15 minutes another 11 **mg** NaH dispersion and 23 **mg** methyl iodide were added. After 15 more minutes aqueous ammonium chloride solution and ethyl acetate were added, and the organic. . . washed with water, 2N NaOH, dried and concentrated giving a viscous oil which was used without further purification: Yield 283 **mg**, 84%.

DETD (3S)-tert-Butoxycarbonylamino-(2R)-hydroxy-4-phenyl-butyric acid (Schweizerhall, Inc., S. Plainfield, N.J., 1.02 g, 3.4 mmol) and dimethylamine hydrochloride (338 **mg**, 4.1 mmol) were coupled

according to Procedure A (0-25.degree. C., dimethylformamide-dichloromethane solvent, acid, then base extraction) giving crude product which was chromatographed on silica eluted with 1-8% ethanol in dichloromethane: Foam; Yield 995 **mg**, 91%;

DETD (1S,2R)-(1-Benzyl-2-methoxy-methyl-carbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (113 **mg**, 0.32 mmol) was dissolved in 4N HCl-dioxane (4 mL) at 25.degree. C. for 1 hour, concentrated, and the residue triturated with ether giving the title product (93 **mg**, 100%).

DETD Sodium hydride dispersion (30 **mg** of 50% in oil) was added to a solution of (1S,2R)-(1-Benzyl-2-methoxy-methyl-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester in tetrahydrofuran (2 mL) at 0.degree. C. After 5 minutes methyl iodide (175 **mg**) was added and the mixture was allowed to stand at 25.degree. C. for 18 hour. Ethyl acetate and saturated aqueous. . . organic layer was separated, washed with water, dried, concentrated, and chromatographed on silica eluting with 10-20% ethyl acetate-hexanes: Yield 113 **mg**, 52%; HPLC (60/40) 6.45 minutes (>96%).

DETD (1R,2S)-[2-Amino-1-(methoxy-methyl-carbamoyl)-3-phenyl-propoxy]-acetic acid benzyl ester hydrochloride (162 **mg**, 0.38 mmol) was coupled with 5-chloro-1H-indole-2-carboxylic acid (71 **mg**, 0.36 mmol) according to Procedure A (0-25.degree. C. reaction temperature) and the crude product purified by chromatography on silica gel. . .

DETD (1R,2S)-[2-tert-Butoxycarbonylamino-1-(methoxy-methyl-carbamoyl)-3-phenyl-propoxy]-acetic acid benzyl ester (170 **mg**, 0.35 mmol) was dissolved in 4N HCl-dioxane (2 mL) for 1.5 hours at 25.degree. C., concentrated, the residue coevaporated with ether and dried giving an oil (163 **mg**). MS 387 (MH+, 100%).

DETD Sodium hydride dispersion (120 **mg** of 50% in oil, 2.8 mmol) was added to a solution of (1S,2R)-(1-benzyl-2-methoxy-methyl-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (858 **mg**, 2.5 mmol) in tetrahydrofuran (8 mL) at 0.degree. C. After effervescence ceased benzyl bromoacetate (0.56 g, 2.5 mmol) was added and the mixture was brought to 25.degree. C. After 2 hours more NaH dispersion was added (12 **mg**), and the mixture was stirred 1 hour, diluted with ethyl acetate and saturated ammonium chloride, the organic layer separated, washed. . . was chromatographed on silica gel eluted with 20-75% ethyl acetate-hexanes. The most pure fractions were combined giving an oil (175 **mg**, 15%): MS 487 (MH+), 387 (100%).

DETD A mixture of [(2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-methyl-carbamoyl)-3-phenyl-propoxy]-acetic acid benzyl ester (120 **mg**, 0.2 mmol) and 50% moist palladium hydroxide on carbon catalyst in methanol (50 mL) was shaken at 40 p.s.i. hydrogen. . . mixture was allowed to stand for 30 min, then filtered through a filter aid and the filtrate concentrated giving 121 **mg** of a solid which was chromatographed on silica and eluted with 25-100% ethyl acetate-hexanes giving 84 **mg** of a solid, HPLC (60/40) 4.81 (37%) and 6.24 minutes (63%). .sup.1 H NMR and MS analysis showed these to. . . separated, washed with water, dried, and concentrated giving a mixture of the title substance and the des-5-Cl analog: Yield 85 **mg**, 71%; HPLC (60/40) 3.49 minutes (37%), 4.23 minutes (61%); MS 338 (MH+, 100%); TSPMS 474/476 (MH+for title substance, 40%), 440. . .

DETD . . . fluoride (0.30 g, 1.29 mmol) was added to a solution of (2S,3S)-3-amino-2-hydroxy-4-phenyl-butyramide hydrochloride (0.319 g, 1.61 mmol) and triethylamine (145 **mg**, 1.42 mmol) in dichloromethane (2 mL) at 25.degree. C. After 18 hours the mixture was diluted with ethyl acetate, the. . .

DETD . . . for 1 hour. The mixture was concentrated and the residue triturated with ether and dried giving a colorless solid (430 **mg**): HPLC (60/40) 2.68 min, 100%.

DETD Aqueous 1N NaOH (2.6 mL) was added to a solution of (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2S)-hydroxy-4-phenylbutyric acid methyl ester

(500 **mg**, 1.29 mmol) in methanol at 25.degree. C. After 18 hours the mixture was concentrated, the residue dissolved in ethyl acetate. . . layer was separated, extracted three times with ethyl acetate, the organic layers combined, dried and concentrated giving a solid (417 **mg**, 87%): HPLC (60/40) 4.23 (>98%).

DETD [1(S)-Benzyl-(2S)-(tert-butyl-dimethyl-silanyloxy)-2-cyano-ethyl]-carbamic acid tert-butyl ester (417 **mg**) was added to a solution of anhydrous HCl (3.2g) in methanol (20 mL) and the resulting solution capped and kept at 25.degree. C. for 5 days. The mixture was concentrated to give 308 **mg** of colorless solid which was homogeneous by .sup.1 H NMR (D.sub.2 O). This material was combined with spectrally equivalent material prepared in the same manner from 400 **mg** of the same precursor, and together the mixture was dissolved in saturated aqueous NaHCO.sub.3 which was extracted ten times with chloroform. The combined extracts were dried and concentrated giving the title substance (328 **mg**, 75%):

DETD A solution of (3S)-[(5-fluoro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid methyl ester (190 **mg**, 0.5 mmol), 1N NaOH (1 mL) and methanol (5 mL) was stirred at 25.degree. C. for 18 hours. The pH. . . water at 25.degree. C. and filtered. The resulting solid was washed with ether and dried giving a colorless glass (160 **mg** , 87%): HPLC (60/40) 3.49 minutes (99%); .sup.1 H NMR (partial, DMSO-d.sub.6) .delta.8.15 (d, 1H, J=8 Hz), 7.42 (m, 2H), 7.3. . .

DETD Aqueous 1N NaOH (1.18 mL) was added to a suspension of (3S)-[(5,6-dichloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid methyl ester (249 **mg**, 0.6 mmol) in methanol (5 mL) at 25.degree. C. After 18 hours the mixture was concentrated, the residue partitioned between. . . washed with ethyl acetate, the combined organic layers washed with brine, dried and concentrated giving a yellow solid: Yield 259 **mg**; HPLC (60/40) 4.96 minutes (100%); TSPMS 407/409 (MH+, 100/40%);

DETD Aqueous 1N NaOH (1.69 mL) was added to a suspension of (3R)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid methyl ester (326 **mg**, 0.8 mmol) in methanol at 25.degree. C. After 2.5 hours the mixture was concentrated (starting material found) and redissolved in. . . and the residue partitioned between excess 2N HCl and ethyl acetate, the organic layer separated, dried and concentrated: Yield 288 **mg**, 92%; HPLC (60/40) 3.89 minutes (93%); mp 215-223.degree. C.; TSPMS 373/375 (MH+, 100%);

DETD (2R,3R)-3-Amino-2-hydroxy-4-phenylbutyric acid methyl ester hydrochloride (239 **mg**, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (200 **mg**, 1.05 mmol) were coupled according to Procedure A (0-25.degree. C., washed with acid, then base) giving crude product which was used without further purification: Yield 328 **mg**, 87%.

DETD A mixture of (2R,3R)-3-amino-2-hydroxy-4-phenylbutyric acid (200 **mg**, 1.0 mmol, Sigma Chemical Co. (St. Louis, Mo.), chlorotrimethylsilane (500 **mg**, 4.6 mmol) and methanol (2 mL) was heated at reflux for 5.5 hours and concentrated to a foam: Yield 244 **mg**, 100%.

DETD A large excess of anhydrous ammonia was introduced into a solution of (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid methyl ester (100 **mg**, 0.27 mmol) in methanol (10 mL) and the mixture was heated in a stainless steel Parr reactor (<50 p.s.i.) for. . .

DETD Dimethylamine hydrochloride (262 **mg**, 3.22 mmol) and (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (1.0 g, 2.68 mmol) were coupled in DMF (4 mL) using triethylamine (530 **mg**, 3.22 mmol), 1-hydroxybenzotriazole hydrate (612 **mg**, 4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 25.degree. C. for 18 hours. The mixture was diluted with chloroform (80 mL) and. . . 10 mL cold ether

and filtered, washing with 5 mL cold ether giving after drying a colorless solid: Yield 715 **mg**, 67%); mp 190-192.degree. C.; HPLC (60/40) 4.53 minutes (100%); FABMS 400/402 (MH+, 80%), 178 (100%);

DETD N-Methylhydroxylamine hydrochloride (167 **mg**, 2.0 mmol) and (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (373 **mg**, 1.0 mmol) were coupled according to Procedure A (DMF solvent, base wash omitted) and the crude product purified by chromatography. . .

DETD . . . Procedure A. The mixture was purified by chromatography on silica eluting with 33-50% ethyl acetate-hexanes giving the title substance (100 **mg**) and the more polar major substance 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide (970 **mg**), plus a mixture of the two substances (159 **mg**, mostly more polar product). For the title substance: PBMS 593/595 (MH+, 60%), 400(100%);

DETD . . . hydrochloride (0.39 mmol) and (3S)-[(5-bromo-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (0.32 mmol) were coupled according to Procedure A (0-25.degree. C.) The crude product (159 **mg**) was stirred with 200 **mg** polystyrene-DMAP resin (Aldrich Chemical Co., Milwaukee, Wis.) in dichloromethane for 1 hour at 25.degree. C., filtered and the filtrate concentrated:. . .

DETD 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC, 790 **mg**, 4.12 mmol), dichloroacetic acid (136 **mg**, 1.06 mmol) and 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide (287 **mg** , 0.69 mmol) were added, in this order, to a solution of anhydrous dimethylsulfoxide (4 mL) and toluene (anhydrous, 4 mL). . . HCl, and saturated aqueous NaHCO.sub.3. The organic layer was dried, concentrated and the resulting foam recrystallized from ether. Yield, 100 **mg** , 35%; HPLC (60/40) 10.72 minutes (87%), starting material eluted at 6.68 minutes in this run and was present at less. . .

DETD {1(R)-[Hydroxy-((S)-methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-carbamic acid (285 **mg**, 0.8 mmol) was dissolved in cold 4N HCl-dioxane and the resulting solution stirred for 1 hour at 0.degree. C. The mixture was concentrated and the residue triturated with ether and dried giving 207 **mg** (90%) of a solid.

DETD (2S,3R)-3-(t-Butoxycarbonylamino)-2-hydroxy-4-phenylbutyric acid (300 **mg**, 1.0 mmol, Sigma Chemical Co., St. Louis, Mo.)) and N,O-dimethylhydroxylamine hydrochloride (104 **mg**, 1.1 mmol) were coupled according to Procedure A (0-25.degree. C. reaction temperature): Yield 88%; HPLC (60/40) 4.90 minutes (95%);

DETD m-Chloroperoxybenzoic acid (62 **mg** of 50%, 0.18 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-(2R)-hydroxy-3-oxo-3-thiazolidin-3-yl-propyl)-amide (80 **mg**, 0.18 mmol) in dichloromethane (2 mL). After 1 hour the mixture was poured into a mixture of saturated aqueous sodium. . . acetate. The organic layers were combined, washed with saturated aqueous sodium bicarbonate, dried, and concentrated giving a yellow solid (80 **mg**, 96%): HPLC (60/40) 3.37 (97%); PBMS 460/462 (MH+, 100%).

DETD m-Chloroperoxybenzoic acid (45 **mg** of 50%, 0.13 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-(2R)-hydroxy-3-oxo-3-thiomorpholin-4-yl-propyl)-amide (60 **mg**, 0.13 mmol) in dichloromethane (1.5 mL). After 1 hour the mixture was poured into a mixture of saturated aqueous sodium. . . title sulfoxide (Example 70) as a yellow solid which was chromatographed on silica gel eluting with 1% ethanol-dichloromethane: Yield 44 **mg**, 72%; HPLC (60/40) 6.14 minutes (98%). PBMS 474/476 (MH+, 100%). A less polar product (8 **mg**) identified as the title sulfone (Example 71) was also isolated: HPLC (60/40) 6.44 minutes (96%). PBMS 490/492 (MH+, 100%).

DETD Lithium hydroxide solution (0.2 mL of 1N in water) was added to a solution of 1-{(3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-

4-phenyl-butyryl}-piperidine-4-carboxylic acid ethyl ester (111 **mg**, 0.22 mmol) in tetrahydrofuran (2 mL) at 25.degree. C. After 18 hours the mixture was concentrated and the residue triturated. . . 6N HCl was added to attain a pH of 1. The organic layer was separated, dried and concentrated giving 109 **mg** (100%) of a solid: HPLC (60/40) 3.79 minutes (99%);

DETD Trifluoroacetic acid (2 mL) was added to a solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-tert-butoxycarbamoyl-hydroxy-methyl)-2-phenyl-ethyl]-amide (256 **mg**, 0.58 mmol) in dichloromethane (2 mL) and the resulting solution was stirred for 18 hours at 25.degree. C. More trifluoroacetic. . . with 2.5%, 5%, 10% ethanol-dichloromethane containing 1% acetic acid. The purified product was triturated with ether-hexanes and dried: Yield 70 **mg**, 31%; HPLC (60/40) 3.11 (96%);

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2R)-hydroxy-4-phenylbutyric acid (310 **mg**, 0.8 mmol) and (1-benzyl-piperidin4-yl)-methyl-amine hydrochloride (EPO publication 0 457 686, example 1A therein, 200 **mg**, 0.8 mmol) were coupled according to Procedure A (dimethylformamide solvent). The crude product was purified by chromatography on silica gel eluted with 0.5-4% ethanol in dichloromethane containing 0.5% ammonium hydroxide giving a colorless foam: yield 140 **mg**, 30%; HPLC (60/40) 4.15 minutes (95%); TSPMS 559/562 (MH+, 100%);

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (1.0 g, 2.6 mmol) and 4-methylamino-piperidine-1-carboxylic acid tert-butyl ester (575 **mg**, 2.6 mmol) were coupled according to Procedure A (dimethylformamide solvent). The crude product was purified by chromatography on silica gel eluted with 20, 30, 40, 50, and 75% ethyl acetate-hexanes: yield 319 **mg**, 21%; HPLC (60/40) 10.31 minutes (94%); 569/571 (MH+, 100%).

DETD 4-({(3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyryl}-methyl-amino)-piperidine-1-carboxylic acid tert-butyl ester (292 **mg**, 0.5 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. and stirred for 1 hour at room temperature. The mixture was concentrated and the residue triturated with ether and dried: yield 249 **mg**, 96%; HPLC (60/40) 2.59 minutes (96%). PBMS 469/471 (MH+, 100%);

DETD Molecular seives (3 .ANG. powdered, 100 **mg**), triethylamine (22 **mg**, 0.2 mmol), glacial acetic acid (64 **mg**, 1.1 mmol), sodum cyanoborohydride (95%,18 **mg**, 0.3 mmol), and aqueous formaldehyde (37 weight % in water, 22 **mg**, 0.3 mmol) were added sequentially to a solution of 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methyl-piperidin4-yl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide hydrochloride (100 **mg**, 0.2 mmol) in methanol (2 mL) at 25.degree. C. After 18 hours the reaction mixture was filtered thru Celite.RTM., the. . . solid residue was purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane giving a colorless solid (93 **mg**, 91%). This material was dissolved in methanol at 0.degree. C., the resulting solution treated with 1.01 N HCl (0.21 mL), and the resulting solution immediately concentrated. The residue was triturated with ether and dried: yield 87 **mg**, 79%; HPLC (60/40) 2.86 minutes (95%); TSPMS 483/485 (MH+, 100%);

CLM What is claimed is:

21. The method as recited in claim 19 for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a therapeutically effective amount of a compound of claim 1.

. . . a glycogen phosphorylase inhibitor as recited in claim 30; b) an antidiabetic agent selected from insulin and insulin analogs; insulinotropin; **Sulfonylureas** and analogs; Biguanides; .alpha.2-Antagonists and Imidazolines; insulin secretagogues;

Glitazones; Fatty Acid Oxidation inhibitors; .alpha.-Glucosidase inhibitors; .beta.-Agonists; Phosphodiesterase Inhibitors; Lipid-lowering Agents; Antiobesity Agents; Vanadate and **vanadium** complexes and peroxovanadium complexes; Amylin Antagonists; Glucagon Antagonists; Gluconeogenesis Inhibitors; Somatostatin Analogs; Antilipolytic Agents; and c) optionally a pharmaceutically acceptable. . .

37. A method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a therapeutically effective amount of a compound of claim 30.

45. A method for treating Type I **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

47. A method for treating Type II **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

49. A method for treating Type II **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

L8 ANSWER 2 OF 3 USPATFULL
PI US 6107329 20000822
WO 9639384 19961212 <--
AB . . . R.sub.9 or C(O)R.sub.12 as glucogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.
SUMM This invention relates to glycogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.
SUMM In spite of the early discovery of insulin and its subsequent widespread use in the treatment of **diabetes**, and the later discovery of and use of **sulfonylureas** (e.g. Chlorpropamide.TM. (Pfizer), Tolbutamide.TM. (Upjohn), Acetohexamide.TM. (E. I. Lilly), Tolazamide.TM. (Upjohn)) and biguanides (e.g. Phenformin.TM. (Ciba Geigy), Metformin.TM. (G. D. Searle)) as oral hypoglycemic agents, the treatment of **diabetes** remains less than satisfactory. The use of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective Type I **diabetes**, insulin dependent **diabetes** mellitus), requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of. . . causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death. Treatment of non-insulin dependent **diabetes** mellitus (Type II **diabetes**, NIDDM) usually consists of a combination of diet, exercise, oral agents, e.g. **sulfonylureas**, and in more severe cases, insulin. However, the clinically available hypoglycemics can have other side effects which limit their use.. . .
SUMM . . . whom the causative agent or disorder is unknown. While such "essential" hypertension is often associated with disorders such as obesity, **diabetes** and hypertriglyceridemia, the relationship between these disorders has not been elucidated. Additionally, many patients display the symptoms of high blood. . .
SUMM This invention is directed to a glycogen phosphorylase inhibitor

compound of Formula I useful for the treatment of **diabetes**, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hypertension, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM Yet another aspect of this invention is directed to a method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a Formula I compound. Included in the treatment of **diabetes** is the prevention or attenuation of long term complications such as neuropathy, nephropathy, retinopathy or cataracts.

SUMM Another aspect of this invention is directed to pharmaceutical compositions for the treatment of **diabetes** which comprise a therapeutically effective amount of a glycogen phosphorylase inhibitor;

SUMM . . . or more antidiabetic agents such as insulin and insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2 ; **Sulfonylureas** and Analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide.RTM., glimepiride, repaglinide, meglitinide; Biguanides: metformin, phenformin, buformin; .alpha.2-Antagonists and Imidazolines: midaglizole, isaglidole,. . . 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243; Phosphodiesterase Inhibitors: L-386,398; Lipid-lowering Agents: benfluorex; Antiobesity Agents: fenfluramine; Vanadate and **vanadium** complexes (e.g. naglivan.RTM.) and peroxovanadium complexes; Amylin Antagonists; Glucagon Antagonists; Gluconeogenesis Inhibitors; Somatostatin Analogs; Antilipolytic Agents: nicotinic acid, acipimox, WAG. . .

SUMM Another aspect of this invention is a method of treating **diabetes** in a mammal with the above described combination compositions.

SUMM . . . glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity. Examples include **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM . . . of 10 g ryptone, 5 g yeast extract, 5 g NaCl, and 1 ml 1N NaOH per liter) plus 100 **mg**/L ampicillin, 100 **mg**/L pyridoxine and 600 **mg**/L MnCl.sub.2 and grown at 37.degree. C. to a cell density of OD.sub.550 =1.0. At this point, the cells are induced. . .

SUMM . . . immobilized on Affi-Gel 10 (BioRad Corp., Melvile, N.Y.) as per the manufacturer's instructions. In brief, the phosphorylase kinase enzyme (10 **mg**) is incubated with washed Affi-Gel beads (1 mL) in 2.5 mL of 100 mM HEPES and 80 mM CaCl.sub.2 at. . .

SUMM . . . PO.sub.4 and 0.5 mM dithiothreitol. 20 .mu.l of this stock is added to 80 .mu.l of Buffer A containing 0.47 **mg**/mL glycogen, 9.4 mM glucose, 0.63 mM of the oxidized form of nicotinamide adenine dinucleotide phosphate (NADP.sup.+). The compounds to be. . . MgCl.sub.2 and 0.5 mM dithiothreitol. 20 .mu.l of this stock is added to 80 .mu.l of Buffer B with 1.25 **mg**/mL glycogen, 9.4 mM glucose, and 0.63 mM glucose-1-phosphate. The compounds to be tested are added as 5 .mu.l of solution. . . L. J., Reinach, P. S. and Candia, O. A. (1979) Anal. Biochem. 100, 95-97] modified as follows: 150 .mu.of 10 **mg**/mL ammonium molybdate, 0.38 **mg**/mL malachite green in 1N HCl is added to 100 .mu.l of the enzyme mix. After a 20 minute incubation at. . .

SUMM . . . (a modification of the method of Richterich and Dauwalder, Schweizerische Medizinische Wochenschrift, 101, 860 (1971)) (hexokinase method) using a 100 **mg**/dL standard. Plasma glucose is then calculated by the equation:

SUMM Plasma glucose (**mg**/dL)=Sample value.times.5.times.1.784=8.92.t imes.Sample value

SUMM The animals dosed with vehicle maintain substantially unchanged hyperglycemic glucose levels (e.g., greater than or equal to 250

mg/dL), animals treated with test compounds at suitable doses have significantly depressed glucose levels. Hypoglycemic activity of the test compounds is. . .

SUMM . . . administered, the animals are sacrificed by decapitation and trunk blood is collected into 0.5 mL serum separator tubes containing 3.6 mg of a 1:1 weight/weight sodium fluoride: potassium oxalate mixture. The freshly collected samples are centrifuged for two minutes at 10,000.times.. . .

SUMM . . . method; a modification of the method of Allain, et al. Clinical Chemistry 20, 470 (1974)) using a 100 and 300 mg/dL standards. Serum insulin, triglycerides, and total cholesterol levels are then calculated by the equations,

SUMM Serum triglycerides (mg/dL)=Sample value.times.2

SUMM Serum total cholesterol (mg/dL)=Sample value.times.2

SUMM The animals dosed with vehicle maintain substantially unchanged, elevated serum insulin (e.g. 225 .mu.U/mL), serum triglycerides (e.g. 225 mg/dl), and serum total cholesterol (e.g. 160 mg /dL) levels, while animals treated with test compounds of this invention generally display reduced serum insulin, triglycerides, and total cholesterol levels.. . .

SUMM . . . BB/W rats, or non-diabetic BB/W age matched control rats are pretreated with heparin (1000 u, i.p.), followed by pentobarbital (65 mg/kg, i.p.). After deep anesthesia is achieved as determined by the absence of a foot reflex, the heart is rapidly excised. . .

SUMM Surgery: New Zealand White male rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 mg/kg, i.v.). A tracheotomy is performed via a ventral midline cervical incision and the rabbits are ventilated with 100% oxygen using. . .

SUMM . . . over, for example 5 minutes and allowing 10 minutes before further intervention or by infusing the adenosine agonist, PIA (0.25 mg/kg). Following ischemic preconditioning, pharmacological preconditioning or no conditioning (unconditioned, vehicle control) the artery is occluded for 30 minutes and then. . .

SUMM . . . lowering activities and hyperinsulinemia reversing activities of the compounds of this invention is in the range of 0.005 to 50 mg/kg/day, preferably 0.01 to 25 mg/kg/day and most preferably 0.1 to 15 mg/kg/day.

DETD . . . with 2N HCl, 2N NaOH, 2N HCl, dried, triturated with 1:1 ether/hexanes and dried, giving an off-white solid: Yield 280 mg , 73%; HPLC (60/40) 4.66 minutes (96%); PBMS 322/324 (MH+, 100%).

DETD . . . sequence was repeated and the resulting solids were suspended in EtOAc, stirred for 1 hour, filtered and dried: Yield 252 mg , 88%; HPLC (60/40) 2.33 minutes (93%); TSPMS 338/340 (MH+, 100%);

DETD . . . filtered and the collected solid washed successively with aqueous 2N HCl, aqueous 2N NaOH, ether and dried : Yield 180 mg , 68%; TSPMS 336/338 (MH+, 100%);

DETD . . . purified by column chromatography on silica gel eluted with 0.5-16% ethanol in dichloromethane to give a colorless foam: Yield 260 mg, 63%; HPLC (60/40) 100%, 3.86 minutes; PBMS 412/414 (MH+, 100%);

DETD . . . residue purified by column chromatography on silica gel eluted with 10, 20 and 30% ethyl acetate in hexanes: Yield 14 mg, 6%; HPLC (60/40) 8.88 minutes (98%); PBMS 398/400 (MH+, 100%);

DETD . . . by column chromatography on silica gel eluted with 30% ethyl acetate in hexanes to give a colorless foam: Yield 290 mg, 95%; HPLC (70/30) 6.23 min (99%); PBMS 512/514 (MH+, 100%);

DETD . . . desired fractions concentrated, the residue dissolved in chloroform and methanol and the resulting solution stirred 18 hours with approx. 128 mg dimethylaminopyridine-polystyrene resin (Fluka Chemical Co.). The solution was filtered, concentrated and the residue triturated with ether: Yield, 51%; HPLC (60/40). . .

DETD . . . reaction temperature). The crude product was dissolved in

chloroform and methanol and the resulting solution stirred 18 hours with 50 **mg** dimethylaminopyridine-polystyrene resin (Fluka Chemical Co.), the solution filtered, concentrated and the solids triturated with ether: Yield 83%; HPLC (60/40) 8.88. . .

DETD . . . acetate, the resulting solution washed with 2N NaOH and 2N HCl, the suspension filtered and the solids dried: Yield 111 **mg**, 26%; HPLC (60/40) 8.88 minutes (92%); PBMS 424/426 (MH+, 100%); mp 258-261.degree. C.; PBMS 424/426 (MH+, 100%);

DETD . . . to procedure A (0-25.degree. C. reaction temperature, 140 hour reaction time) and the crude product triturated with ether: Yield 89 **mg**, 71%; HPLC (70/30) 7.57 minutes (98%); PBMS 396/398 (MH+, 100/80%);

DETD . . . the product purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane containing 0.5% ammonium hydroxide: Yield 86 **mg**, 69%; HPLC (40/60) 7.57 minutes (>99%); mp 187-190.5.degree. C.; TSPMS 441/443 (MH+, 100%);

DETD . . . Na.sub.2 SO.sub.4, and concentrated. The residue was stirred under ether for 1 hour, the solid filtered and dried: Yield 125 **mg**, 87%; HPLC (60/40) 2.85 minutes (98%); PBMS 469/471 (MH+, 100/90%);

DETD . . . temperature, 60 hour reaction time, washed first with acid, then base), and the resulting solid triturated with ether: Yield 320 **mg**, 99%; HPLC (60/40) 5.87 minutes (100%);

DETD . . . ethyl acetate and 2N NaOH, the resulting suspension filtered, the solids washed with ethyl acetate, water and dried: Yield 135 **mg**, 40%; HPLC (40/60) 7.29 minutes (98%); TSPMS 338/340 (MH+, 100%);

DETD . . . according to Procedure A and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate-hexanes: Yield 241 **mg**, 50%; HPLC (60/40) 7.67 minutes (94%);

DETD . . . with 0.20 mL 4N HCl in dioxane. A precipitate formed which was filtered, washed with dichloromethane and dried: Yield 220 **mg**, 42%; HPLC (60/40) 3.19 minutes (96%);

DETD . . . according to Procedure A and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate-hexanes: Yield 302 **mg**, 59%; PBMS 511/513 (MH+, 100%);

DETD . . . to Procedure A. The resulting solid was suspended in ether, filtered and dried to give a beige solid: Yield, 264 **mg**, 71%; HPLC (60/40) 3.28 minutes (100%); TSPMS 322/324 (MH+, 100%);

DETD . . . (1.0 mmol) were coupled according to Procedure A. The resulting solid was suspended in ether, filtered and dried: Yield 158 **mg**, 53%; PBMS 296/298 (MH+, 100%);

DETD . . . on silica gel eluted with 5-30% ethanol in dichloromethane containing 0.5% ammonium hydroxide, followed by trituration with ether: Yield 21 **mg**, 5%; PBMS 453/455 (MH+, 100%);

DETD . . . layer separated and washed with brine, dried over Na.sub.2 SO.sub.4, concentrated and the resulting solid triturated with ether: Yield 189 **mg**, 77%; HPLC (60/40) 2.63 minutes (99%);

DETD . . . The resulting solution was stirred at 25.degree. C. for 0.5 hours, concentrated and the residue triturated with ether: Yield 190 **mg**, 85%; HPLC (60/40) 2.62 minutes (98%); PBMS 411/413 (MH+, 100%);

DETD . . . reaction was concentrated and the residue triturated first with ether then with a mixture of ether and hexanes. Yield 360 **mg**, 82%; HPLC (60/40) 4.84 minutes (99%); PBMS 440/442 (MH+, 40%), 396/398 (MH-44, 100%);

DETD . . . to Procedure A and the crude product purified by chromatography on silica gel eluting with 1:2 ethyl acetate-hexanes: Yield 611 **mg**, 62%; HPLC (60/40) 13.45 minutes (57%) and 14.46 minutes (41%).

DETD . . . reaction solvent dimethyl4ormamide). The crude product was stirred in ether for 0.5 hours then filtered giving a beige solid: 182

mg, 98%; HPLC (60/40) 3.41 minutes (98%); mp >260.degree. C. (dec); TSPMS 363/365 (MH+, 100%);

DETD (S)-(1-Methylcarbamoyl-2-thiazol4-yl-ethyl)-carbamic acid tert-butyl ester (248 mg, 0.87 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. The resulting mixture was stirred for 1 hour at 25.degree.. . .

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature, acid wash omitted) and the product used without further purification. Yield, 250 mg, 88%.

DETD . . . product purified by chromatography on silica gel eluted with 10, 20, 40 and 60% ethyl acetate in hexanes: Yield 565 mg, 95%; HPLC (60/40) 3.46 minutes (98%); mp 153-155.degree. C.; TSPMS 297/299 (MH+, 100/40%);

DETD . . . to Procedure A (0-25.degree. C. reaction temperature) and the crude product triturated first with 1:1 ether-hexanes,then with hexanes. Yield 115 mg, 75%; HPLC (60/40) 3.72 minutes (99%); mp 198-202.degree. C. (shrinks on insertion at 192.degree. C.); PBMS 377/379 (MH+, 100%);

DETD . . . the product purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane containing 0.5% ammonium hydroxide. Yield 124 mg, 41%.

DETD . . . to Procedure A and the product purified by chromatography on silica gel eluted with 2-10% ethanol in dichloromethane. Yield 180 mg, 86%; HPLC (60/40) 3.14 minutes (98%); TSPMS 428/430 (MH+, 100%);

DETD . . . purified by chromatography on silica gel eluted with 25, 40, 50, 75 and 100% ethyl acetate in hexanes. Yield 330 mg, 94 %; HPLC (60/40) 4.18 minutes (97%); TSPMS 450/452 (MH+, 100%).

DETD . . . residue was purified by chromatography on silica gel eluted with 1-50% ethanol in dichloromethane containing 0.5% ammonium hydroxide. Yield 217 mg, 80%.

DETD . . . with acid only) and the product purified by chromatography on silica gel eluted with 1-4% ethanol in dichloromethane. Yield 516 mg, 52%; HPLC (60/40) 5.33 minutes (93%).

DETD . . . acetate and 2N NaOH, the resulting precipitate was collected and washed with 2N NaOH, 1N HCl and water. Yield 135 mg, 42%; HPLC (60/40) 2.97 minutes (97%); PBMS 322 (MH+, 100%);

DETD . . . by chromatography on silica gel eluted with 20, 30, 40, 50, 75 and 100% ethyl acetate in hexanes. Yield 228 mg, 84%; HPLC (60/40) 3.57 minutes (98%); PBMS 410 (MH+, 100%);

DETD . . . purified by chromatography on silica gel eluted with 20, 30, 40, 50 and 75% ethyl acetate in hexanes. Yield 189 mg, 95%; HPLC (60/40) 4.76 minutes (97%); PBMS 414 (MH+, 100%);

DETD . . . suspension stirred at 25.degree. C. for 1 hour. The mixture was concentrated and the residue triturated with ether. Yield, 776 mg, 88%; HPLC (60/40) 2.31 minutes (99%).

DETD . . . product purified by chromatography on silica gel eluted with 20, 30, 40 and 50% ethyl acetate in hexanes. Yield 404 mg, 94%; HPLC (60/40) 4.74 min (98%); PBMS 430 (MH+, 100%);

DETD . . . C. The solution was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether. Yield, 866 mg, 84%.

DETD . . . by chromatography on silica gel eluted with 20, 30 and 40% ethyl acetate in hexanes giving a colorless foam (979 mg, 89% yield).

DETD . . . washed with 2N HCl, 2N NaOH and water. The filtered solid was boiled in acetone, filtered and dried. Yield 134 mg, 40%; HPLC (60/40) 3.06 minutes (97%); mp 239-241.degree. C. (with discoloration); PBMS 340 (MH+, 70%), 357 (100%)

DETD . . . acid (40 mL) and cooled giving a solid which was filtered, washed with cold ethyl acetate and dried: Yield 980 mg (70%); HPLC (60/40) 3.09 minutes (97%).

DETD . . . mmol) were coupled according to Procedure A (0-25.degree. C. reaction temperature) and the product triturated with 1:1 ether-hexanes. Yield 213 **mg**, 92%; HPLC (60/40) 4.15 minutes (99%); PBMS 412 (MH+, 100%);

DETD . . . the resulting precipitate was collected by filtration followed by washing with 2N HCl, 2N NaOH, water and ether. Yield 110 **mg**, 52%; HPLC (60/40) 3.37 minutes (99%); mp 236-239.degree. C. (dec); PBMS 356/358 (MH+, 100%);

DETD . . . ethyl acetate and 2N HCl, filtered, and the filtered solid washed with 2N HCl, 2N NaOH and ether. Yield 988 **mg**, 98%; HPLC (70/30) 3.25 minutes (99%); mp 253-255.degree. C. (dec, darkening at 243.degree. C.); PBMS 324/326 (MH+, 100%);

DETD . . . gel eluted with 50, 75 and 100 % ethyl acetate in hexanes followed by trituration from 1:1 ether-hexanes. Yield 266 **mg**, 76%; HPLC (60/40) 4.09 minutes (99%); PBMS 426/428 (MH+, 100%);

DETD . . . ethyl acetate in hexanes. The product was collected as an off-white foam and triturated with 1:1 ether-hexanes to give 107 **mg**, 73%; HPLC (60/40) 6.21 minutes (99%); PBMS 490/492 (MH+, 100%):

DETD . . . eluted with 40 and 50% ethyl acetate in hexanes, followed by trituration of the resulting foam with ether. Yield 112 **mg**, 45%; HPLC (60/40) 5.13 minutes (>99%); PBMS 410/412 (MH+, 100%);

DETD (S)-[1-Benzyl-2-oxo-2-(3-oxo-pyrrolidin-1-yl)-ethyl]-carbamic acid tert-butyl ester (552 **mg**, 1.7 mmol) was dissolved in 4M HCl-dioxane (6.2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether to give alight brown solid. Yield, 482 **mg**, 108%.

DETD . . . reaction time, washed with acid first then base). The crude product was triturated with 1:1 ether-hexanes and dried. Yield 966 **mg**, 91%; HPLC (60/40) 7.99 minutes (97%); PBMS 414/416 (MH+, 100%);

DETD . . . silica gel eluted with 30, 40 and 50% ethyl acetate in hexanes followed by trituration with 1:1 ether-hexanes. Yield 266 **mg**, 75%; HPLC (60/40) 5.52 minutes (>99%); PBMS 446/448 (MH+, 100%);

DETD . . . the product purified by chromatography on silica gel eluted with 50, 75 and 100% ethyl acetate in hexanes. Yield 362 **mg**, 86%; HPLC (60/40) 5.06 minutes (97%); mp 227-229.degree. C.; TSPMS 460/462 (MH+, 100%);

DETD (S)-[1-(4-Chloro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl)-carbamic acid tert-butyl ester (475 **mg**, 1.2 mmol) was dissolved in 4M HCl-dioxane (5 mL) at 0.degree. C. The mixture was stirred for 1.5 hour at 25.degree. C., concentrated and the residue triturated with ether. Yield, 422 **mg**, 105%; TSPMS 283 (MH+, 100%).

DETD . . . Procedure A and the product purified by chromatography on silica gel eluted with 1:1 and 3:1 ethyl acetate/hexanes. Yield 662 **mg**, 69%.

DETD . . . the residue purified by chromatography on silica gel eluted with 5-20% ethanol in dichloromethane containing 0.5% ammonium hydroxide. Yield 232 **mg**, 81%; HPLC (40/60) 2.57 minutes (98%); PBMS 416/418 (MH+, 100%);

DETD (S)-{2-(4-Hydroxy-piperidin-1-yl)-2-oxo-1-[1-(toluene-4-sulfonyl)-1H-imidazol-4-ylmethyl]-ethyl}-carbamic acid tert-butyl ester (512 **mg**, 1.0 mmol) was dissolved in 4 M HCl-dioxane (3 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1.5 hours, concentrated and the residue triturated with ether. Yield, 422 **mg**, 105%; TSPMS 283 (MH+, 100%).

DETD 4-Hydroxypiperidine (303 **mg**, 3.0 mmol), triethylamine (394 **mg**, 3.9 mmol) and diethyl cyanophosphonate (636 **mg**, 3.9 mmol) were added in that order to Boc-N.sub.im -tosyl-L-histidine (J Med Chem 30 536 (1987); 1.32 g, 3.9 mmol). . . dried and concentrated. The residue was purified by chromatography on silica gel

eluted with 1-8% ethanol in dichloromethane. Yield, 517 **mg**, 35%; HPLC (50/50) 4.75 minutes (97%).

DETD . . . chromatography, along with the more polar serine analog (40%) on silica gel eluted with 1-16% ethanol in dichloromethane. Yield 51 **mg**, 16%; HPLC (60/40) 7.06 minutes (96%); PBMS 348/350 (100%), 543/545 (MH+, <5%).

DETD (S)-[1-Hydroxymethyl-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (595 **mg**, 2.0 mmol) was dissolved in 4M HCl-dioxanes (2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether. Yield, 506 **mg**, 105%; MS 189 (MH+, 100%)

DETD . . . extracts were concentrated and the residue purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane. Yield 751 **mg**, 41%; HPLC (40/60) 2.72 minutes (96%).

DETD . . . dried and concentrated. The residue was purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane. Yield, 150 **mg**, 52%; HPLC (60/40) 3.53 minutes (99%); PBMS 442/444 (MH+, 100%);

DETD (S)-[1-(4-Hydroxy-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (450 **mg**, 1.2 mmol) was dissolved in 4M HCl-dioxane (2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether. Yield, 400 **mg**, 107%; MS 265 (MH+, 100%).

DETD . . . foam was purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane containing 0.5% NH.sub.4 OH. Yield 550 **mg**, 41%; HPLC (40/60) 5.02 minutes (87%).

DETD . . . C. reaction temperature) and the product purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane. Yield 26 **mg**, 8%; HPLC (50/50) 5.02 minutes (99%); PBMS 427/429 (MH+, 100%);

DETD (S)-[2-(4-Hydroxy-piperidin-1-yl)-2-oxo-1-pyridin-3-ylmethyl-ethyl]-carbamic acid-tert-butyl ester (367 **mg**, 1.05 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. The resulting suspension was stirred for 1.5 hours at 25.degree. C., concentrated and the residue triturated with ether. Yield, 450 **mg**, 100%.

DETD . . . acid wash omitted) and the product purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane. Yield 454 **mg**, 46%; MS 350 (MH+, 100%).

DETD . . . purified by chromatography on silica gel eluted with 25, 30, 50, 75 and 80% ethyl acetate in hexanes. Yield 150 **mg**, 60%; HPLC (60/40) 3.66 minutes (97%); mp 204-207.degree. C.; PBMS 410 (MH+, 100%);

DETD . . . 0.degree. C. The solution was stirred 2 hours at 25.degree. C., concentrated and the residue triturated with ether. Yield, 920 **mg**, 124%; HPLC (60/40) 2.23 minutes (98%).

DETD . . . (R)-N-t-Boc-p-fluoro-phenylalanine (3.5 mmol) were coupled according to Procedure A giving a foam which was used without further purification. Yield 940 **mg**, 73%; HPLC (60/40) 3.64 minutes (95%); MS 367(MH+, 100%).

DETD . . . crude product purified by chromatography on silica gel eluted with 50, 75 and 100% ethyl acetate in hexanes. Yield 171 **mg**, 765%; HPLC (60/40) 4.23 minutes (97%); MS 444/446 (MH+, 100%); TSPMS 444/446 (MH+, 100%);

DETD . . . hexanes. The resulting solid was boiled in ethyl acetate, the resulting suspension filtered, and the collected solid dried. Yield 103 **mg**, 48%; HPLC (60/40) 3.69 minutes (95%); PBMS 428 (MH+, 100%);

DETD . . . the product purified by chromatography on silica gel eluted with 20, 30 and 50% ethyl acetate in hexanes. Yield, 26 **mg**, 8%; HPLC (60/40) 8.14 minutes (98%); PBMS 546/548 (MH+, 100%);

DETD . . . temperature, 1:1 dichloromethane/DMF reaction solvent) and the

product purified by chromatography on silica gel eluted with ethyl acetate. Yield 313 **mg**, 65%; HPLC (60/40) 2.84 minutes (99%); TSPMS 387/389 (MH+, 100%);

DETD . . . The resulting solution was stirred for 2 hours at 25.degree. C., concentrated and the residue triturated with ether. Yield, 390 **mg**, 95%.

DETD . . . 2:1 dichloromethane/dimethylformamide reaction solvent, acid wash omitted, Na.sub.2 SO.sub.4 used for drying). The residue was triturated with ether giving 428 **mg** (86% yield) of a yellow solid.

DETD . . . and 40% ethyl acetate in hexanes. The residue was triturated with 1:1 ether-hexanes, and hexanes giving an off-white solid (484 **mg**, 63%): HPLC (60/40) 8.13 minutes (95%); TSPMS 375/377 (MH+, 100%);

DETD . . . resulting solution was brought to reflux for 1 hour, cooled and concentrated. The residue was triturated with ether. Yield, 515 **mg**, 100%; HPLC (60/40) 2.31 minutes (95%).

DETD . . . was purified by chromatography on silica gel eluted with 10, 20, 30 and 40% ethyl acetate in hexanes. Yield 375 **mg**, 80%; HPLC (60/40) 6.36 minutes (99%); PBMS 392/394 (MH+, 100%);

DETD . . . 25.degree. C. for 2 hours. The mixture was concentrated and the residue triturated with ether giving a yellow solid (321 **mg**, 96%; HPLC (60/40) 2.24 minutes (98%); MS 215 (MH+, 100%).

DETD . . . coupled according to Procedure A (0-25.degree. C. reaction temperature) giving the product which was used without further purification. Yield 426 **mg**, 104%.

DETD . . . eq). After 5 minutes, the reaction mixture was concentrated and the residue triturated with ether giving and orange solid (79 **mg** , 29% yield): TSPMS 385/387 (MH+, 100%);

DETD (S)-[2-(4-Amino-phenyl)-1-dimethylcarbamoyl-ethyl]-carbamic acid tert-butylester (214 **mg**, 0.7 mmol) was dissolved in 4M HCl-dioxane (2 mL) at 0.degree. C. and the solution stirred for 2 hours at 25.degree. C. The mixture was concentrated and the residue triturated with ether. Yield, 294 **mg**, 102%; PBMS 208 (MH+, 100%).

DETD . . . was purified by chromatography on silica gel eluted with 50, 60, 70 and 100% ethyl acetate in hexanes. Yield 226 **mg**, 42%; HPLC (70/30) 2.45 minutes (100%).

DETD . . . by chromatography on silica gel eluted with 10, 20, 30, 40, 50 and 60% ethyl acetate in hexanes. Yield 263 **mg**, 90%; HPLC (60/40) 7.12 minutes (99%); TSPMS 384/386 (MH+, 100%);

DETD (S)-(1-Dimethylcarbamoyl-3-phenyl-propyl)-carbamic acid tert-butyl ester (235 **mg**, 0.8 mmol) was dissolved in 4 M HCl-dioxane (2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1.5 hours, concentrated and the residue triturated with ether. Yield, 187 **mg**, 100%; HPLC (60/40) 2.31 minutes (99%).

DETD . . . A (0-25.degree. C. reaction temperature, 3:1 dichloromethane/DMF reaction solvent) giving the product which was used without further purification. Yield 238 **mg**, 93%; HPLC (60/40) 5.98 minutes (97%).

DETD . . . silica gel eluted with 20, 40, 50 and 75% ethyl acetate in hexanes followed by trituration with ether. Yield 400 **mg**, 104%; HPLC (60/40) 3.93 minutes (98%); mp 228-231.degree. C. (dec, yellowed at 210.degree. C.); TSPMS 386/388 (MH+, 100%);

DETD . . . were coupled according to Procedure A. The residue was triturated with ether to give a light yellow solid. Yield, 160 **mg**, 36%; mp 210-213.degree. C. (dec); PBMS 372/374 (MH+, 100%);

DETD [(1S)-(Methoxy carbamoyl)-2-phenyl-ethyl]-carbamic acid tert-butyl ester (200 **mg**, 0.68 mmol) was dissolved in 4 M HCl-dioxane at 0.degree. C. and the mixture stirred at 25.degree. C. After 0.5. . .

DETD . . . A (0-25.degree. C. reaction temperature). The crude product was triturated with dichloromethane and then with ether and dried. Yield 236 **mg**, 79%; HPLC (60/40) 4.63 minutes (97%); PBMS 356/358 (MH+,

100%);

DETD (R)-(1-Methylcarbamoyl-2-phenyl-ethyl)-carbamic acid tert-butyl ester (722 **mg**, 2.6 mmol) was dissolved in 4M HCl-dioxane (10 mL) at 0.degree. C. The mixture was stirred for 1 hour at 25.degree. C., concentrated and the residue triturated with ether. Yield, 517 **mg**, 93%.

DETD . . . hour reaction time, washed with acid first, then base) giving the product which was used without further purification. Yield 760 **mg**, 96%.

DETD . . . (0-25.degree. C. reaction temperature, 96 hour reaction time). The crude product was triturated with 1:1 ether-hexanes and dried. Yield 24 **mg**, 96%; HPLC (60/40) 8.05 minutes (97%); PBMS 405/407 (MH+, 100%);

DETD . . . with 6N HCl and extracted with ethyl acetate. The extracts were dried and concentrated giving a light brown solid (458 **mg**, 34%): HPLC (60/40) 5.31 (93%).

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature) and the resulting foam triturated with 1:1 ether/hexanes and dried. Yield 374 **mg**, 90%; HPLC (60/40) 6.17 minutes (98%); mp 199-201.degree. C.; PBMS 414/416 (MH+, 100%);

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature). The crude product was triturated with 1:1 ether-hexanes and dried. Yield 302 **mg**, 87%; HPLC (60/40) 5.46 minutes (99%); mp 198.5-200.degree. C.; PBMS 350 (MH+, 100%);

DETD . . . to Procedure A (0-25.degree. C. reaction temperature, 60 hour reaction time) and the resulting foam triturated with ether. Yield 329 **mg**, 90%; HPLC (60/40) 4.27 minutes (99%); PBMS 366 (MH+, 100%);

DETD . . . to Procedure A (0-25.degree. C. reaction temperature, 60 hour reaction time) and the resulting solid triturated with ether. Yield 320 **mg**, 91%; HPLC (60/40) 4.74 minutes (100%); mp 229.5-232.degree. C.; PBMS 354 (MH+, 100%);

DETD . . . (0-25.degree. C. reaction temperature) and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate/hexanes. Yield 38 **mg**, 66%; HPLC (60/40) 4.08 minutes (97%); PBMS 361 (MH+, 100%);

DETD . . . acid (40 mL) and cooled giving a solid which was filtered, washed with cold ethyl acetate and dried: Yield 980 **mg** 70%; HPLC (60/40) 3.09 minutes (97%).

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature). The resulting solid was triturated with hexanes, then with ether. Yield 272 **mg**, 81%; HPLC (70/30) 3.49 minutes (99%); mp 199-200.degree. C.; PBMS 336 (MH+, 100%);

DETD . . . hour reaction time) and the crude product purified by column chromatography on silica gel eluted with ethyl acetate. Yield 150 **mg**, 37%; HPLC (60/40) 3.08 minutes (96%);

DETD (3S,4S)-[1-Benzyl-2-(3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (360 **mg**, 1.00 mmol) was dissolved in 4 M HCl-dioxane (4 ml) at 25.degree. C. for 3 hours. The mixture was concentrated and the resulting yellow solid triturated with ether and dried. Yield 304 **mg**, 103%.

DETD Boc-L-phenylalanine (2.2 mmol) and (3S,4S)-dihydroxy-pyrrolidine (U.S. Pat. No. 4,634,775, example 1C, 206 **mg**, 2.0 mmol) were coupled according to procedure A (0-25.degree. C. reaction temperature) giving a colorless solid which was used without further purification. Yield 431 **mg**, 61%.

DETD 2(S)-Amino-1-((3RS)-hydroxy-piperidin-1-yl)-3-phenyl-propan-1-one hydrochloride (570 **mg**, 2.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (429 **mg**, 2.2 mmol) were coupled according to procedure A (5:2 dichloromethane-dimethylformamide solvent) and the crude product triturated with 1:1 ether-hexanes. The. . . column chromatography on silica gel eluted with 3:2, and 2:1 ethyl acetate/hexanes followed by trituration with 1:1 ether/hexanes. Yield

430 **mg**, 51%: HPLC (60/40) 3.45 minutes (95%);

DETD 4-((2S)-Amino-3-phenyl-propionyl)-piperazin-2-one hydrochloride (140 **mg**, 0.5 mmol) and 5-chloro-1H-indole-2-carboxylic acid (98 **mg**, 0.5 mmol) were coupled according to procedure A and the crude product purified by column chromatography on silica gel eluted with ethyl acetate and 2% ethanol in ethyl acetate followed by trituration with ether. Yield 71 **mg**, 33%: HPLC (60/40) 3.53 minutes (100%); PBMS 425/427 (MH+, 100%);

DETD [(1S)-Benzyl-2-oxo-2-(3-oxo-piperazin-1-yl)-ethyl]-carbamic acid tert-butyl ester (400 **mg**, 1.2 mmol) was dissolved in 4M HCl-dioxane (10 ml) at 25.degree. C. for 0.5 hours. The mixture was concentrated and the residue co-evaporated with dichloromethane, triturated with ether, and dried. Yield 340 **mg**, 103%.

DETD BOC-L-phenylalanine (530 **mg**, 2 mmol) and piperazin-2-one (J. Am. Chem. Soc. 62 1202 (1940), 200 **mg**, 2 mmol) were coupled according to procedure A (2:1 dichloromethane/dimethylformamide reaction solvent, washed with 1 N NaOH after acid washes) and the product used without further purification. Yield 404 **mg**, 58%.

DETD (2S)-Amino-1-morpholin-4-yl-propan-1-one hydrochloride (195 **mg**, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (195 **mg**, 1.0 mmol) were coupled according to procedure A (washed with 1N NaOH after acid washes) giving crude product which was triturated with ether and dried. Yield 150 **mg**, 45%: HPLC (60/40) 3.61 minutes (100%); PBMS 336/338 (MH+, 100%);

DETD BOC-L-Alanine (3.50 **mg**, 20 mmol) and morpholine (1.74 g, 20 mmol) were coupled according to procedure A (washed with 1N NaOH after acid. . .

DETD (2S)-Amino-N-methyl-3-phenyl-propionamide hydrochloride (214 **mg**, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (195 **mg**, 1.0 mmol) were coupled according to procedure A and the crude product triturated with ether and dried. Yield 160 **mg**, 45%: HPLC (60/40) 4.60 minutes (100%);

DETD BOC-L-phenylalanine (2.65 g, 10 mmol) and methylamine hydrochloride (675 **mg**, 10 mmol) were coupled according to procedure A (washed with 1N NaOH after acid washes) yielding the title compound as. . .

DETD (2S)-Amino-N-methoxy-N-methyl-propionamide hydrochloride (169 **mg**, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (195 **mg**, 1.0 mmol) were coupled according to procedure A (washed with 1 N NaOH after acid washes) giving the product (290 **mg**, 94%): HPLC (60/40) 4.03 minutes (94%); PBMS 310/312 (MH+, 100%);

DETD L-phenylalaninamide hydrochloride (835 **mg**, 4.17 mmol) and 5-bromo-1H-indole-2-carboxylic acid (1.0 g, 4.17 mmol) were coupled according to procedure A substituting the following workup: the. . . filtered and the collected solid washed with ethyl acetate, 2 N NaOH, 2 N HCl, ether, and dried. Yield 890 **mg**; PBMS 386/388 (MH+, 100%);

DETD (2S)-Amino-N-methoxy-N-methyl-3-phenyl-propionamidehydrochloride (317 **mg**, 1.3 mmol) and 5-chloro-1H-indole-2-carboxylic acid (253 **mg**, 1.3 mmol) were coupled according to procedure A (0-25.degree. C., washed first with acid, then base). The crude product was. . . and 40% ethyl acetate in hexanes. The foam obtained was triturated with isopropyl ether yielding an off white solid (356 **mg**, 71%): HPLC (60/40) 8.28 minutes (98%);

DETD Racemic 2-amino-2-methyl-3-phenyl-propionic acid methyl ester (200 **mg**, 0.87 mmol) and 5-chloro-1H-indole-2-carboxylic acid (170 **mg**, 0.87 mmol) were coupled according to Procedure A (2:1 dichloromethane/dimethylformamide solvent) and the product purified by chromatography on silica gel eluted with 10% ethyl acetate in hexanes. Yield 286 **mg**, 89%; HPLC (60/40) 9.63 minutes (85%); TSPMS 371/373 (MH+, 100%);

DETD Aqueous 2N LiOH (0.10 ml, 0.50 mmol) was added to a solution of (2RS)-[(5-chloro-1H-indole-2-carbonyl)-amino]-2-methyl-3-phenyl-

propionic acid methyl ester (132 **mg**, 0.36 mmol) in tetrahydrofuran (8 ml) at 25.degree. C. The resulting solution was stirred for 1 hour, concentrated and the. . . organic layer was separated, washed with water, brine and dried giving a foam which was used without further purification (129 **mg**, 102%): HPLC (60/40) 4.42 minutes (99%); TSPMS 357/359 (MH+, 100%);

DETD m-Chloroperoxybenzoic acid (80 **mg** of 50%, 0.23 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-2-oxo-2-thiomorpholin-4-yl-ethyl)-amide (100 **mg**, 0.23 mmol) in dichloromethane (2 mL). After 1 hour, the mixture diluted with ethyl acetate and washed three times with. . .

DETD m-Chloroperoxybenzoic acid (202 **mg** of 50%, 0.58 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-2-oxo-2-thiomorpholin-4-yl-ethyl)-amide (100 **mg**, 0.23 mmol) in dichloromethane (2 mL). After 1 hour, the mixture was diluted with ethyl acetate and the resulting solution. . .

DETD m-Chloroperoxybenzoic acid (167 **mg** of 50%, 0.48 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-2-oxo-2-thiazolidin-3-yl-ethyl)-amide (200 **mg** , 0.48 mmol) in dichloromethane (4 mL). After 0.5 hours, the mixture was diluted with ethyl acetate and washed three times. . . on silica gel eluted with 1-8% ethanol in dichloromethane and then triturated with ether giving the title compound. Yield 151 **mg** (73%); HPLC (60/40) 3.64 minutes (98%); PBMS 430/432 (MH+, 100%);

DETD Hydroxylamine hydrochloride (68 **mg**, 0.82 mmol) and potassium carbonate (136 **mg**, 0.98 mmol) were added to a solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-oxo-2-(3-oxo-pyrrolidin-1-yl)-ethyl]-amide in ethanol (5 ml) and water (1 ml) at. . .

DETD Yield 48 **mg** (14%); HPLC (60/40) 4.69 minutes (97%); mp 216-220.degree. C. (darkened at 210.degree. C.); PBMS 425/427 (MH+, 100%).

DETD Yield 69 **mg** (20%); HPLC (60/40) 6.78 minutes (>99%); mp 223-224.degree. C. (dec, tar); PBMS 425/427 (MH+, 100%);

DETD . . . 30%, 40%, 50%, 75% and 100% ethyl acetate in hexane giving partial separation. The pure fractions were pooled giving 31 **mg** (25%) of the title substance: HPLC (60/40) 9.38 minutes (94%); PBMS 410/412 (MH+, 100%);

DETD [(5-Chloro-1H-indole-2-carbonyl)-amino]-acetic acid methyl ester (100 **mg**, 0.40 mmol) was added to a saturated solution of ammonia in methanol (ca. 3 mL) at 25.degree. C. The suspension. . . was sonicated for 1 hour and the resulting solution concentrated. The residue was triturated with ether/hexanes and dried. Yield 77 **mg** , 77%; HPLC (60/40) 2.78 minutes (98%); PBMS 252/254 (MH+, 100%);

DETD Trifluoroacetic acid was added to a solution of 1-{(2S)-[(5-bromo-1H-indole-2-carbonyl)-amino]-3-phenyl-propionyl}-pyrrolidine-(2S)-carboxylic acid tert-butyl ester (345 **mg**, 0.64 mmol) in dichloromethane (2 ml) at 0.degree. C. After 1 hour at 25.degree. C., the reaction mixture was concentrated, triturated with ether and dried giving a yellow solid. Yield 273 **mg**, 88%; HPLC (70/30) 4.75 minutes (98%); TSPMS 484/486 (MH+, 100%);

DETD L-phenylalanine-L-proline tert-butyl ester (333 **mg**, 1.0 mmol) and 5-bromo-1H-indole-2-carboxylic acid were coupled according to procedure A (72 hour reaction time). The product was purified by. . . column chromatography on silica gel eluted with 15%, 20% and 30% ethyl acetate giving a pale yellow foam. Yield 428 **mg** (79%); HPLC (70/30) 5.84 minutes (81%).

DETD m-Chloroperoxybenzoic acid (426 **mg** of 50%, 1.2 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid (2-oxo-2-thiazolidin-3-yl-ethyl)-amide (400 **mg**, 1.2 mmol) in dichloromethane (8 mL) at 25.degree. C. After 1 hour, the mixture was diluted with ethyl acetate (ca. . .

DETD Excess aqueous 2 M LiOH was added to a solution of 1-{(2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-3-phenyl-propionyl}-(4R)-hydroxy-pyrrolidine-(2S)-carboxylic acid benzyl ester (215 **mg**, 0.40 mmol) in tetrahydrofuran at 25.degree. C. After 2 hours, the mixture was diluted with ethyl acetate and ice and. . . and the organic layers combined and dried. The residue was triturated with ether and dried giving a colorless solid (190 **mg**, 106%): HPLC (60/40) 3.43 minutes (94%); TSPMS 456/458 (MH+, 100%);

DETD A solution of 3-{[(5-chloro-1H-indole-2-carbonyl)-amino]-acetyl}-thiazolidine-2-carboxylic acid methyl ester (196 **mg**, 0.5 mmol) in methanol (10 mL) was treated with aqueous 1 N NaOH (0.5 mL) at 25.degree. C. After 3. . . organic layers were combined, dried, and concentrated giving a solid which was triturated with 1:1 ether-hexane and dried. Yield 186 **mg**, 99%; HPLC (60/40) 3.13 minutes (98%); TSPMS 368/370 (MH+, 70%), 339 (100%).

DETD . . . silica gel eluted with 25%, 50%, 75% and 100% ethyl acetate-hexanes giving the title substance as a colorless foam (104 **mg**, 22%). A mixture (180 **mg**) of less polar products was also isolated. Title substance: HPLC (60/40) 4.18 minutes (97%); TSPMS 398/400 (MH+, 100%);

DETD [(1S)-Benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (515 **mg**, 1.6 mmol) was dissolved in cold 4N HCl-dioxane, the mixture stirred 2 h at 25.degree. C., concentrated, and the residue coevaporated with ether giving a colorless solid (415 **mg**, 100%).

DETD A solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-oxo-azetidin-1-yl)-2-oxo-ethyl]-amide (product of Example 170, 50 **mg**, 0.13 mmol), sodium acetate trihydrate (43 **mg**, 0.32 mmol) and hydroxylamine hydrochloride (18 **mg**, 0.25 mmol) in methanol (2 mL) was heated at reflux for 8 h and concentrated. The residue was partitioned between. . . The organic layer was separated and dried giving a colorless solid which was triturated with ether-hexanes and dried (yield 36 **mg**, 69%): HPLC (50/50) 6.74 min (99%); TSPMS 411/413 (MH+, 10%), 180 (100%); .sup.1 H NMR (DMSO-d.sub.6) .delta. 11.75 (br, 1H),. . .

DETD A mixture of 5-chloro-1H-indole-2-carboxylic acid [1(S)-benzyl-2-oxo-2-(4-oxo-piperidin-1-yl)-ethyl]-amide (406 **mg**, 0.96 mmol) , hydroxylamine hydrochloride (80 **mg**, 1.15 mmol), and potassium carbonate, (159 **mg**, 1.15 mmol) in ethanol (6 mL) and water (1 mL) was stirred at 25.degree. C. for 18 h and concentrated. The residue was dissolved in ethyl acetate and the resulting solution washed with water and dried (411 **mg**, 98%): HPLC (60/40) 5.13 minutes (97%); TSPMS 439/441 (MH+, 100%);

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide (Example 46, 669 **mg**) was added in one portion at 0.degree. C. to a mixture of 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (DEC, 1.80 g, 9.4 mmol) and dichloroacetic acid (307 **mg**, 1.5 mmol) in anhydrous toluene (e mL) and anhydrous dimethylsulfoxide (e mL). The mixture was stirred at 0-20.degree. C. for. . . the residue purified by chromatography on silica gel eluted with 25%, 50%, and 75% ethyl acetate-hexanes giving a foam (424 **mg**, 64%).

DETD [(1S)-Benzyl-2-(1,3-dihydro-isoindol-2-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (88 **mg**) was dissolved in cold 4N HCl-dioxane (1.5 mL), stirred 2 h at 25.degree. C., and the mixture concentrated. The residue was triturated with ether and dried (65 **mg**, 91%). TSPMS 267 (MH+, 100%).

DETD . . . the product purified by chromatography on silica gel eluted with 20% and 50% ethyl acetate-hexanes giving an amber oil (88 **mg**, 23%): TSPMS 367 (MH+, 100%).

DETD . . . eluted with 20%, 30%, 40% and 50% ethyl acetate in hexane giving the title substance as a colorless foam (600 **mg**, 47%):

HPLC (60/40) 5.09 minutes (98%); TSP-MS 396 (MH+, 100%); 1H NMR (CDCl.sub.3) .delta. 9.14 (br, 1H), 7.62 (d, 1H,. . .

DETD [(1S)-Benzyl-2-oxo-2-(3-oxo-azetidin-1-yl)-ethyl]-carbamic acid tert-butyl ester (297 **mg**, 0.9 mmol) was dissolved in 4N HCl-dioxane (3 mL). The resulting solution was stirred at 25.degree. C. for 2 h, concentrated, and the residue triturated with ether and dried (196 **mg**, 82%).

DETD [(1S)-Benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (320 **mg**, 1 mmol) was added in one portion to a mixture of 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (DEC, 575 **mg**, 3 mmol) and dichloroacetic acid (192 **mg** , 1.5 mmol) in anhydrous toluene (2 mL) and anhydrous dimethylsulfoxide (2 mL). The mixture was stirred at 0-20.degree. C. for. . . solution washed twice with 1 N HCl, twice with saturated aqueous NaHCO.sub.3, dried and concentrated giving a colorless solid (304 **mg**, 96%).

DETD . . . coupled according to Procedure A and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate-hexanes (235 **mg**, 63%): HPLC (60/40) 4.92 min (91%); PBMS 371/373 (MH+, 100%); .sup.1 H NMR (CDCl.sub.3) .delta. 11.25 (br, 0.6H), 10.9 (br,. . .

DETD . . . were coupled according to Procedure A (3:1 dimethylformamide-dichloromethane reaction solvent) and the product triturated with 2:1 ether-hexanes and dried (130 **mg**, 63%): HPLC (60/40) 6.22 minutes (95%); TSPMS 429/431 (45%, MH+NH3), 412/414 (30%, MH+), 325/327 (100%). .sup.1 H NMR (DMSO-d6) .delta.. . .

CLM What is claimed is:

36. The method as recited in claim 34 for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a compound of claim 1.

L8 ANSWER 3 OF 3 USPATFULL

TI Complexed **vanadium** for the treatment of **diabetes** mellitus

PI US 5300496 19940405 <--

SUMM **Diabetes** is a mammalian condition in which the amount of glucose in the blood plasma is abnormally high. The condition can be life-threatening and high glucose levels in the blood plasma (hyperglycemia) can lead to a number of chronic **diabetes** syndromes, for example, atherosclerosis, microangiopathy, kidney disorders, renal failure, cardiac disease, diabetic retinopathy and other ocular disorders including blindness.

SUMM . . . automatically in a complex procedure that involves, inter alia, the hormone insulin. In diabetics, external intervention is needed. Treatment of **diabetes** is now carried out using several drugs. Insulin is the mainstay of treatment; it replaces the natural hormone produced in the pancreas. In **diabetes**, insulin is not produced in sufficient quantities, or the body becomes resistant to insulin and requires more than normal amounts. . .

SUMM Oral **diabetes** medications are available. **Sulfonylureas** depend on insulin release in the body and are therefore not effective in patients who cannot make their own insulin.. . .

SUMM . . . by Cantley and co-workers to be a potent inhibitor of Na.sup.+ -K.sup.+ ATPase (1). The same group showed that vanadate (**vanadium**+5) taken up by the red blood cells was reduced to **vanadium** +4 in the form of vanadyl ion V=O.sup.2+ in the cytoplasm (2).

SUMM Since the above work, there has been a significant focus on the effects of **vanadium**, mostly as vanadate, on glucose metabolism and uptake into cells. A natural outgrowth of this work has been the study of **vanadium** and **diabetes** (3).

SUMM . . . vanadyl sulfate will also lower blood glucose and blood lipids in STZ diabetic rats and will prevent secondary complications of

diabetes such as cataracts and cardiac dysfunction. Vanadyl sulfate is less toxic than the vanadate form of **vanadium** but is also poorly absorbed There have only been two attempts to modify the biological uptake of **vanadium** by changing the chemical form in which it is supplied from either vanadate (VO.sub.4.sup.3-) or vanadyl sulfate (VOSO.sub.4.(H.sub.2 O).sub.x), which has been used because the active form of **vanadium** may be the vanadyl ion. Work on **vanadium** peroxides has been carried out by Posner et al. (12,13) and U.S. Pat. No. 4,882,171 to Fantus and Posner was issued on Nov. 21, 1989. It relates to **vanadium**-peroxide compositions as insulin mimics. This work involves in vitro studies of co-administered vanadate and peroxide.

SUMM . . . issued Mar. 1, 1989 to Lazaro et al. describes and claims a vanadyl cysteine compound for the oral treatment of **diabetes**. The compound in the European patent has the structure: ##STR1##

SUMM There is a need for medication, preferably to be taken orally, that is effective in the treatment of **diabetes** Accordingly, the present invention provides a pharmaceutical composition useful for lowering blood sugar and depressing appetite in a mammal, the composition comprising a **vanadium** compound of the formula:

SUMM Preferably, the **vanadium** compound has a structure selected from: ##STR3## in which R is as defined above and R.sub.1 is the balance of. . .

SUMM . . . present invention is also a method of lowering blood sugar in a mammal that comprises administering to the mammal a **vanadium** compound of the general formula:

DETD . . . pharmacological effectiveness of the compound. Using male rats, made diabetic by the injection of STZ at a dose of 60 **mg**/kg i.v., the compound was initially given by intraperitoneal (i.p.) injection as a suspension in 1% methyl cellulose.

DETD Nine out of the twelve rats given 15 **mg**/kg i.p (0.05 mmol/kg) responded to the compound with a decrease in blood glucose. Two animals developed hypoglycemia.

DETD a. Drinking. Administration of the vanadyl compound in the drinking water at doses of 0.46-0.92 mmol/kg (150-300 **mg**/kg, using concentrations of 0.5-1.3 **mg**/mL) reduced blood glucose in four diabetic rats into the normal range. Fluid intake was also decreased to normal in these. . .

DETD . . . Control-Treated (11 animals), Diabetic (11 animals) and Diabetic-Treated (12 animals). The diabetic state was induced by injecting STZ at 60 **mg**/kg dissolved in 0.9% NaCl I.V. via the tail vein to anaesthetised rats. The two control groups were injected with 0.9%. . .

DETD . . . began with a 3.17 mM solution of the compound. On day 6, the concentration was reduced to 1.58 mM (0.5 **mg**/ml). On day 24, the concentration was increased to 2.37 mM (0.7 **mg**/ml). At this point 8 out of the 12 animals were responding to the compound.

DETD The present invention provides a pharmaceutical composition useful for the treatment of **diabetes** mellitus, or an appetite suppressant, or both. The active compounds are absorbed across the gastrointestinal barrier and deliver the vanadyl ion to the bloodstream, where the insulin-mimetic properties of **vanadium** can be expressed. In contrast to insulin, the compositions are active when taken by mouth, and represent a significant advance in **diabetes** therapy. The compositions are also useful as orally active appetite suppressants and would be effective in treating obesity. The majority. . .

DETD 2. Cantley, L.C. Jr. and Aisen, P. "The fate of cytoplasmic **vanadium** implications on (Na,K)-ATPase inhibition." J. Biol. chem. 254:1781-1784, 1979.

DETD 3. Reviewed in Shechter, Y. "Insulin-mimetic effects of vanadate: possible implications for future treatment of **diabetes** "

Diabetes 39:1-5, 1990.

DETD . . . "Detection of oxovanadium(IV) and characterization of its ligand environment in subcellular fractions of the liver of rats treated with pentavalent **vanadium**(V)." Biochem. Biophys. Res. Comm. 96:293-298,1980.

DETD 7. Ramanadham, S., Mongold, J.J., Brownsey, R.W., Cros, G.H. and McNeill, J.H. "Oral vanadyl sulfate in treatment of **diabetes** mellitus in rats". Amer. J. Physiol. 257:H904-H911, 1989.

DETD 9. Pederson, R.A., Ramanadham, S., Buchan, A.M.J. and McNeill, J. "Long term effects of vanadyl treatment on streptozotocin-induced **diabetes** in rats". **Diabetes** 38(11):1390-1395, 1989.

DETD 11. Ramanadham, S., Heyliger, C., Gresser, M.J. Tracey, A.S. and McNeill, J.H. "The distribution and half-life for retention of **vanadium** in the organs of normal and diabetic rats orally fed **vanadium**(IV) and **vanadium**(V)." Biol. Trace Elements (in press) 1991.

DETD 12. Kadota, S. et al. "Peroxide(s) of **vanadium** a novel and potent insulin-mimetic agent which activates the insulin receptor kinase " Biochem. Biophys. Res. Comm. 147:259-266,1987.

DETD 17. Jungnickel, J.E. and Klinger, W. "Photometrische bestimmung von **vanadium** mit 2-methyl-3-hydroxy- -pyron(maltol)." Z. Anal. Chem. 203:257-260, 1964.

CLM What is claimed is:

. . . method as claimed in claim 1 in which the bis(maltotao)oxovanadium(IV) is administered by injection at a dose of about 15 **mg**/kg.

. . . as claimed in claim 4 in which the bis(maltolato)oxovanadium(IV) is administered orally at a dose in the range of 150-300 **mg**/kg.